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Functional Food Synergies: improving the effect of the omega-3 fatty acid docosahexaenoic acid on cardiovascular disease risk factors through concurrent dietary consumption of canola or soy isoflavones

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Functional Food Synergies: Improving the effect of the omega-3 fatty acid docosahexaenoic acid on cardiovascular disease risk factors through concurrent dietary consumption of canola or soy isoflavones.

A thesis submitted in (partial) fulfilment of the
requirements for the award of the degree

DOCTOR OF PHILOSOPHY (PhD)

From

UNIVERSITY OF WOLLONGONG

By

Leisa Ridges (BSc Hons)

School of Health Sciences
2007

Certification

I, Leisa Anne Ridges, declare that this thesis, submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Health Sciences, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

Leisa Anne Ridges

14 September 2007

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List of Abbreviations

AA	Arachidonic acid
ALA	Alpha linolenic acid
CAD	Coronary artery disease
CHD	Coronary heart disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
DHAc-s	Daily DHA-rich oil supplementation for twelve weeks with concurrent consumption of control cereal for the first six weeks followed by consumption of soy cereal between six and twelve weeks of the intervention period.
DHAs-c	Daily DHA-rich oil supplementation for twelve weeks with concurrent consumption of soy cereal for the first six weeks followed by consumption of control cereal between six and twelve weeks of the intervention period.
DPA	Docosapentaenoic acid
FXR	Farnesol X receptor
HDL	High density lipoprotein
HNF-4α	Hepatocyte nuclear factor 4α
IDL	Intermediate density lipoprotein
LCAT	Lecithin-cholesterol acyltransferase
LDL	Low denisty lipoprotein
LXR	Liver X receptor
OOc-s	Daily olive oil supplementation for twelve weeks with concurrent consumption of

	control cereal for the first six weeks followed by consumption of soy cereal between six and twelve weeks of the intervention period.
OOs-c	Daily olive oil supplementation for twelve weeks with concurrent consumption of soy cereal for the first six weeks followed by consumption of control cereal between six and twelve weeks of the intervention period.
PPAR	Peroxisome proliferator - activated receptor
SBP	Systolic blood pressure
SR-B1	Scavenger receptor B class-1
SREBP	Sterol regulatory element binding protein

Abstract

Ischaemic heart disease and cerebrovascular disease are among the leading causes of death in Australian men and women with heart diseases being the third highest cause of death in Australian women and fourth highest cause of death in Australian men (AIHW, 2006). In Australia more than 50% of all adults have two or three (out of a possible nine) risk factors for cardiovascular disease and 15% having four or more risk factors.

It has long been recognised that diet modification can reduce these risks. Recently dietary advice has moved from an "exclusionary" to an "inclusionary" paradigm. That is, rather than identify dietary items to avoid, current guidelines recommend incorporating advice to increase the consumption of a range of functional foods including marine sourced omega-3 fatty acids EPA and DHA and vegetable oils.

EPA and DHA are effective functional foods in reducing CVD mortality, cardiac death, sudden death and myocardial infarction. EPA and DHA provide this cardiovascular benefit by improving several risk factors including: fasting plasma triglycerides, blood pressure and arterial compliance. However, a safety concern of dietary EPA and DHA supplementation is their capacity to cause a significant increase in LDL cholesterol concentrations.

Dietary intake levels of EPA and DHA in the Australian diet are well below those associated with reductions in CVD risk. In 50% of the population a potential 20 – fold increase in EPA and DHA would be required to increase intake levels to those commensurate with reduced CVD risk.

While dietary supplementation with EPA and DHA is one means of increasing dietary intake levels, strategies to increase the efficacy of EPA and DHA would also be advantageous and could reduce supplement doses. Dietary strategies that could simultaneously counteract the rise in LDL cholesterol caused by DHA would also be beneficial.

The research described in this thesis aimed to modify the bioavailability and cardiovascular effects of DHA by modifying other dietary factors and combining DHA with other active ingredients. To address these aims two human clinical trials were conducted. The first examined the effect of altering the types of oil and margarine consumed in the diet with view to reducing the dietary intake of omega-6 fatty acids while supplementing the diet with DHA-rich fish oil (MOFO study). This study showed that replacing usual dietary oil and margarine with canola products while supplementing the diet with 1.1g/d of DHA favourably improved total omega-3 fatty acid incorporation and reduced the omega-6: omega-3 fatty acid ratio in plasma and erythrocyte membrane phospholipids as effectively as double the supplement dose of DHA. Additionally, there was a similar rise in erythrocyte membrane and plasma DHA when either safflower or sunola oil, which contain very different amounts of linoleic acid, were consumed concurrently with a daily dietary supplementation of 1.1g/d of DHA. A distinguishing feature of canola is its relatively high omega-3 ALA content. Thus, these findings add to the body of scientific evidence supporting the view that the total amount of dietary omega-3 consumed has greater impact on the bioavailability of supplemented DHA than the ratio of dietary omega-6: omega-3 fatty acids.

The MOFO study also showed that the combination of canola plus 1.1g/d of DHA is equally as effective as daily supplementation with 2.2g/d of DHA at reducing fasting plasma triglyceride concentrations with the added benefit of preventing the significant rise in both LDL and total cholesterol caused by both doses of DHA alone. While further research is warranted based on the findings from animal studies, it can reasonably be proposed that the findings from the MOFO study may be an example of a synergistic effect of canola phytosterols and DHA, rather than ALA and DHA, working together to significantly reduce fasting plasma triglyceride concentrations while preventing detrimental effects on LDL cholesterol in people with mild hypertriglyceridemia.

The second human clinical trial conducted as part of this thesis examined the effect of combining omega-3 fatty acids with soy isoflavones on fasting blood lipids, blood pressure and arterial compliance (Omega-Soy study). The Omega-Soy study showed that the

combined consumption of DHA with soy isoflavones resulted in an 8-10% improvement in HDL cholesterol, an 18-20% reduction in plasma triglyceride concentrations and the absence of a 10.8% rise in LDL cholesterol observed with DHA supplementation alone. Furthermore, the increases in LDL and total cholesterol observed with DHA supplementation in the first six weeks were reversed and significantly reduced when soy cereal was concurrently consumed. The results showed that the dietary combination of soy isoflavones and DHA improve the lipid profile of moderately hyperlipidemic individuals more favourably than either constituent alone.

While further research is warranted based on evidence from *in vitro* cell culture and *in vivo* animal models demonstrating functional effects of soy isoflavones and DHA on lipid metabolism pathways, it can reasonably be proposed that the findings from the Omega-Soy study demonstrate a synergistic effect of soy isoflavones and DHA, working together to significantly reduce fasting plasma triglyceride concentrations without detrimental effects on LDL cholesterol in people with mild hyperlipidemia.

The findings from this thesis support two functional food synergies for effective improvement of blood lipid concentrations when consumed as part of the usual diet of men and postmenopausal women with moderately elevated blood lipids. These functional food combinations are DHA with canola and DHA with soy isoflavones. The findings of this thesis sheds some light on how isoflavones may be actively involved in reducing plasma cholesterol concentrations when consumed with soy protein or in soy containing foods, furthermore the findings of this thesis provide strategies for ultimately reducing the negative side effects of dietary DHA supplementation and for achieving a better outcome in overall lipid profile improvements than could be achieved with DHA supplementation alone. Future research into these synergistic combinations of functional food ingredients with DHA may lead to new directions in functional food development by food manufacturers to enable more consumers to manage their blood lipid concentrations with minimal or without drug therapy requirements.

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